FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 5/1272US

U S APPLICATION NO (If known, see 37 CFR 1 5): To be assigned 10/089024

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/09146	19 September 2000	23 September 1999

TITLE OF INVENTION: Substituted Piperazine Derivatives, the Preparation Thereof and Their Use as Medicaments

APPLICANT(S) FOR DO/EO/US: LEHMANN-LINTZ, Thorsten, HECKEL, Armin; THOMAS, Leo; MARK, Michael

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☑ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☑ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☑ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☑ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☑ Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☑ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☑ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☑ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☑ Other items or information:
    Certified Copy of 199 45 594.5
    Initial Information Data Sheet

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
To be assigned 10/089024	PCT/EP00/09146	5/1272US

	CALCULATIONS PTO USE ONLY	
21. ☑ The following fees are submitted:		
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☑ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	12 - 20 =	0	x **$18.00**	$ .00	
Independent claims	2 - 3 =	0	x **$80.00**	$ .00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$ 270.00	
TOTAL OF ABOVE CALCULATIONS =				$	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +				$ 0.00	
SUBTOTAL =				$ 1260.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☑ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$ 130.00	
TOTAL NATIONAL FEE =				$ 1390.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$	
				Amount to be refunded:	$
				charged:	$ 1390.00

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☑ Please charge my Deposit Account No. 02-2955 in the amount of $ 1390.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2955 . A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

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SIGNATURE

Anthony P. Bottino

NAME

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REGISTRATION NUMBER

INITIAL INFORMATION DATA SHEET

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Customer Number or Barcode Label:

28505

PATENT TRADEMARK OFFICE

PATENT TRADEMARK OFFICE

Application Information:

Title Line One:	Substituted Piperazine Derivatives, the Preparation
Title Line Two:	Thereof and their use as Medicaments
Total Drawing Sheets:	0
Formal Drawings?:	No
Application Type:	Utility
Docket No.:	5/1272US

Continuity Information:

Prior Foreign Applications:

Foreign Application One:	PCT/EP00/09146
Filing Date:	September 19, 2000
Country:	DE
Priority Claimed:	YES

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Lehmann-Lintz, T. et al	)Art Unit:	To be assigned
Serial No.:	To be Assigned	)Examiner:	To be assigned
Filed:	March 14, 2002		
Docket No.:	5/1272US		
Title:	Substituted Piperazine Derivatives, the Preparation Thereof and Their Use as Medicaments		

BOX PCT
Commissioner For Patents
Washington, D.C. 20231

Sir:

Please enter the following amendments and consider the following remarks before commencing examination of the above-captioned patent application.

In the Specification

Page 1, after the title, please insert

--Related Application Data

This application claims priority PCT/EP 00/09146 and is a national stage case filed under 35 USC 371--

In the claims:

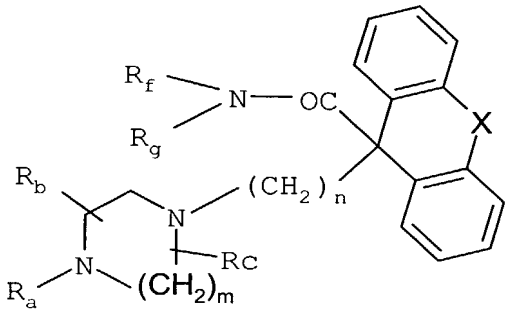
Cancel claims 1-10

Please add the following new claims:

Docket no. 5/1272US

CLEAN SET OF NEW CLAIMS

--11 (New). A compound of the formula (I)



, (I)

wherein

n denotes the number 1, 2, 3, 4 or 5,

m denotes the number 2 or 3,

X denotes a carbon-carbon bond, an oxygen atom, a methylene, ethylene, imino or N-(C_{1-3}-alkyl)-imino group,

R_a denotes a phenyl group or heteroaryl group substituted by the groups R_1 and R_2, wherein

> R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, a hydroxy group, a C_{1-4}-alkoxy group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, a phenoxy, heteroaryloxy, phenyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, nitro, amino, C_{1-3}-alkylamino,

di-(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkyl-amino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group, wherein the abovementioned phenyl or heteroaryl moieties of the group R_1 are optionally substituted by one to five fluorine, chlorine or bromine atoms, a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, a hydroxy group, or a C_{1-4}-alkoxy group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, and

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, or a C_{1-4}-alkoxy group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, or

R_1 and R_2 together represent a methylenedioxy group,

or R_a denotes a monocyclic heteroaryl or phenyl group which is substituted in each case by a phenyl or monocyclic heteroaryl group, while the abovementioned phenyl groups and heteroaryl groups are optionally in each case substituted by a fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group,

R_b and R_c independently of one another denote a hydrogen atom or a C_{1-3}-alkyl group and

R_f and R_g, which are identical or different, denote hydrogen atoms, C_{1-6}-alkyl groups wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, C_{3-7}-cycloalkyl groups, phenyl, heteroaryl, phenyl-C_{1-3}-alkyl or heteroaryl-C_{1-3}-alkyl groups, while the abovementioned phenyl groups and heteroaryl groups are optionally in each case be substituted by one to three fluorine, chlorine or bromine atoms, by one to

three C_{1-3}-alkyl groups wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, by one to three hydroxy groups, one to three C_{1-3}-alkoxy groups wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, or by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, N,N-di-(C_{1-3}-alkyl)-amino, nitro or amino group, or

R_f and R_g together with the nitrogen atom between them denote a 3- to 7-membered cycloalkyleneimino group, while the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group is optionally replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group,

wherein the tricyclic group in the abovementioned formula I are mono- or disubstituted by fluorine or chlorine atoms, by methyl or methoxy groups and the substituents are identical or different,

and wherein the abovementioned heteroaryl groups in this claim are 6-membered heteroaryl groups containing one, two or three nitrogen atoms, or 5-membered heteroaryl groups containing one to four heteroatoms selected from nitrogen, oxygen and sulphur, while hydrogen atoms bound to nitrogen is optionally replaced by C_{1-3}-alkyl groups,
or
the isomers or the salts thereof.

12 (New). The compound according to claim 11, wherein

n denotes the number 3, 4 or 5,

m denotes the number 2 or 3,

X denotes a carbon-carbon bond, an oxygen atom, a methylene, ethylene, imino or N-(C_{1-3}-alkyl)-imino group,

R_a denotes a phenyl group or heteroaryl group substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, a hydroxy group, a C_{1-4}-alkoxy group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, a phenoxy, heteroaryloxy, phenyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkyl-amino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group, wherein the abovementioned phenyl or heteroaryl moieties of the group R_1 are optionally substituted by one to five fluorine, chlorine or bromine atoms, a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, a hydroxy group, or a C_{1-4}-alkoxy group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, and

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, or a C_{1-4}-alkoxy group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, or

R_1 and R_2 together represent a methylenedioxy group,

or R_a denotes a monocyclic heteroaryl or phenyl group which is substituted in each case by a phenyl or monocyclic heteroaryl group, wherein the abovementioned phenyl groups and heteroaryl groups are optionally in each case be substituted by a fluorine, chlorine or

bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, by a hydroxy or C_{1-3}-alkoxy group,

R_b and R_c independently of one another denote a hydrogen atom or a C_{1-3}-alkyl group and

R_f and R_g, which are identical or different, denote hydrogen atoms, C_{1-6}-alkyl groups wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, C_{3-7}-cycloalkyl groups, phenyl, heteroaryl, phenyl-C_{1-3}-alkyl or heteroaryl-C_{1-3}-alkyl groups, wherein the abovementioned phenyl groups and heteroaryl groups are optionally in each case be substituted by one to three fluorine, chlorine or bromine atoms, by one to three C_{1-3}-alkyl groups wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, by one to three hydroxy groups, one to three C_{1-3}-alkoxy groups wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, or by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, N,N-di-(C_{1-3}-alkyl)-amino, nitro or amino group, or and

R_f and R_g together with the nitrogen atom between them denote a 3- to 7-membered cycloalkyleneimino group, wherein the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group is optionally replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group.

13. The compound according to claim 11, wherein

n denotes the number 3, 4 or 5,

m denotes the number 2 or 3,

X denotes a carbon-carbon bond or an oxygen atom,

R_a denotes a phenyl group or heteroaryl group substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, a hydroxy group, a C_{1-4}-alkoxy group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, a phenoxy, heteroaryloxy, phenyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkyl-amino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group, wherein the abovementioned phenyl or heteroaryl moieties of the group R_1 are optionally substituted by one to five fluorine, chlorine or bromine atoms, a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, a hydroxy group, or a C_{1-4}-alkoxy group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, and

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, or a C_{1-4}-alkoxy group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, or

R_1 and R_2 together represent a methylenedioxy group,

or R_a denotes a monocyclic heteroaryl or phenyl group which is substituted in each case by a phenyl or monocyclic heteroaryl group, wherein the abovementioned phenyl groups and heteroaryl groups are optionally in each case be substituted by a fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, by a hydroxy or C_{1-3}-alkoxy group,

R_b and R_c independently of one another denote a hydrogen atom or a methyl group and

R_f denotes a hydrogen atom, a C_{1-6}-alkyl group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, a C_{3-7}-cycloalkyl group, phenyl, heteroaryl, phenyl-C_{1-3}-alkyl or heteroaryl-C_{1-3}-alkyl group, while the abovementioned phenyl groups and heteroaryl groups are optionally in each case be substituted by one to three fluorine, chlorine or bromine atoms, by one to three C_{1-3}-alkyl groups wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, by one to three hydroxy groups, one to three C_{1-3}-alkoxy groups wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, or by a nitro or amino group, and

R_g denotes a hydrogen atom.

14(New). The compound according to claim 11, wherein

n denotes the number 4,
m denotes the number 2,

X denotes a carbon-carbon bond or an oxygen atom,

R_a denotes a phenyl group or heteroaryl group substituted by the groups R_1 and R_2, wherein

> R_1 denotes a hydrogen, fluorine or chlorine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, a C_{1-4}-alkoxy group, a phenoxy group, a phenyl-C_{1-3}-alkoxy or a nitro or amino group,
>
> wherein the abovementioned phenyl moiety of the phenoxy group is optionally substituted by a chlorine atom or by a methoxy group,

R_2 denotes a hydrogen atom, a chlorine atom or a C_1-C_4-alkoxy group,

or R_a denotes a monocyclic heteroaryl or phenyl group which is substituted in each case by a phenyl group,

R_b and R_c independently of one another denote a hydrogen atom or a C_{1-3}-alkyl group and

R_f denotes a C_1-C_6-alkyl group wherein the hydrogen atoms are optionally wholly or partly replaced by fluorine atoms, a phenyl-C_{1-3}-alkyl group, while the abovementioned phenyl group is optionally substituted in each case by a fluorine atom or by a C_1-C_3-alkoxy group, and

R_g denotes a hydrogen atom.

15(New). A compound chosen from

9-[4-(4-biphenyl-3-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide and

9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

or the isomers and the salts thereof.

16(New). A physiologically acceptable salt of the compound according to claim 11.

17(New). A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to claim 11 with one or more pharmaceutically acceptable inert carriers and/or diluents.

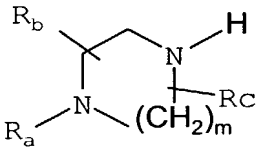
18(New). A method of a lowering plasma levels of atherogenic lipoproteins in a patient, said method comprising administering to a patient in need thereof a pharmaceutically effective amount of a compound according to claim 11.

19(New). A method of treating a disease selected from hyperlipidaemias, atherosclerosis and the clinical sequela thereof, diabetes mellitus, adiposity and pancreatitis, said method comprising administering to a patient in need thereof a pharmaceutically effective amount of a compound according to claim 11.

20(New). The method according to either of claims 18 or 19 wherein the compound according to claim 11 is combined with another lipid-lowering agent.

21(New). Process for preparing a compound of the formula (I) according to claim 1, comprising

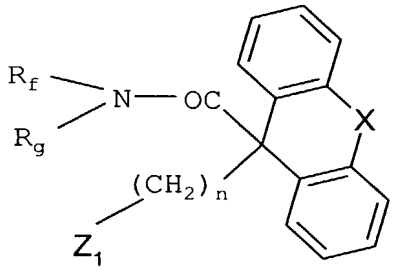
a) reacting under suitable conditions a compound of formula



, (II)

wherein

R_a, R_b and R_c are defined as in claims 1, with a compound of formula



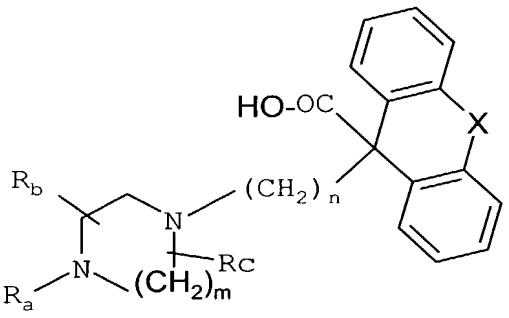
, (III)

wherein

n, R_f, R_g and the tricyclic system are defined as in claims 1 and

Z_1 denotes a nucleofugic leaving group, or

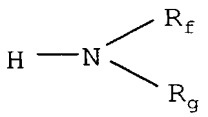
b) reacting under suitable conditions a compound of formula



, (IV)

wherein

the tricyclic system is defined as in claims 1, with an amine of formula



, (V)

wherein

R_f and R_g are defined as in claims 1, or with the reactive derivatives thereof and

c) optionally reducing under suitable conditions the product of a) or b) which contains a nitro group if desired into a corresponding amino compound and/or

d) if R_f denotes a hydrogen atom alkylating under suitable conditions the product into a corresponding compound wherein R_f denotes a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group, and/or

e) cleaving under suitable conditions any protecting group using to protect reactive groups during the reactions and/or

resolving the product any of the product above into its stereoisomers and/or

converting any of the products above into the physiologically acceptable salts thereof.--

Docket no. 5/1272US

REMARKS

Claims 1-10 have been canceled. Claims 11-21 are now pending. Canceled claims 1-10 have been rewritten as new claims 11-21 to be in accordance with US practice. No new matter has been added by way of amendment.

Attached is a marked up copy to show changes to the specification.

Respectfully submitted,

Anthony P. Bottino
Attorney for Applicant(s)
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" EXPRESS MAIL" LABEL NO.:EL 747494492US
DEPOSIT DATE: March 14, 2002
I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO:
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WASHINGTON D.C. 20231

BY 
Anthony P. Bottino, Reg. No. 41,629

Docket no. 5/1272US

Marked Up Copy of Changes:

In the specification:

Page 1, after the title, the following has been inserted:

--Related Application Data

This application claims priority PCT/EP 00/09146 and is a national stage case filed under 35 USC 371--

In the claims:

Claims 1-10 have been canceled.

New claims 11-21 have been added.

77631fft.205

Boehringer Ingelheim Pharma KG
D-55216 Ingelheim/Rhein

Case 5/1272-Fl
Foreign filing text

Substituted piperazine derivatives, the preparation thereof and their use as medicaments

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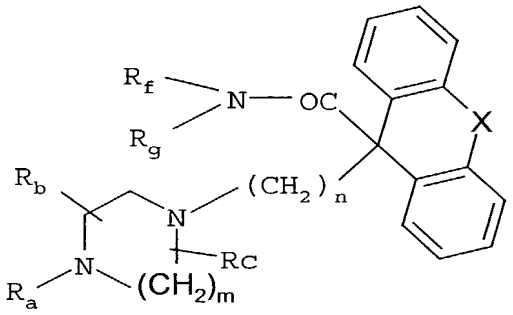
The present invention relates to substituted piperazine derivatives of general formula



, (I)

their isomers, their salts, particularly the physiologically acceptable salts thereof which have valuable pharmacological properties.

The compounds of the above general formula I are valuable inhibitors of the microsomal triglyceride-transfer protein (MTP) and are therefore suitable for lowering the plasma level of the atherogenic lipoproteins.

In the above general formula I

n denotes the number 1, 2, 3, 4 or 5,

m denotes the number 2 or 3,

X denotes a carbon-carbon bond, an oxygen atom, a methylene, ethylene, imino or N-(C_{1-3}-alkyl)-imino group,

R_a denotes a phenyl group or heteroaryl group substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a hydroxy group, a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a phenoxy, heteroaryloxy, phenyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkyl-amino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonyl-amino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group, while the abovementioned phenyl or heteroaryl moieties of the group R_1 may be substituted by one to five fluorine, chlorine or bromine atoms, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a hydroxy group, or a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, and

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or

R_1 and R_2 together represent a methylenedioxy group,

or R_a denotes a monocyclic heteroaryl or phenyl group which is substituted in each case by a phenyl or monocyclic heteroaryl group, while the abovementioned phenyl groups and heteroaryl groups may in each case be substituted by a fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group,

R_b and R_c independently of one another denote a hydrogen atom or a C_{1-3}-alkyl group and

R_f and R_g, which may be identical or different, denote hydrogen atoms, C_{1-6}-alkyl groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, C_{3-7}-cycloalkyl groups, phenyl, heteroaryl, phenyl-C_{1-3}-alkyl or heteroaryl-C_{1-3}-alkyl groups, while the abovementioned phenyl groups and heteroaryl groups may in each case be substituted by one to three fluorine, chlorine or bromine atoms, by one to three C_{1-3}-alkyl groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, by one to three hydroxy groups, one to three C_{1-3}-alkoxy groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, N,N-di-(C_{1-3}-alkyl)-amino, nitro or amino group, or

R_f and R_g together with the nitrogen atom between them denote a 3- to 7-membered cycloalkyleneimino group, while the methylene group in the 4 position of a 6- or 7-membered

cycloalkyleneimino group may additionally be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group,

while the tricyclic group in the abovementioned general formula I may be mono- or disubstituted by fluorine or chlorine atoms, by methyl or methoxy groups and the substituents may be identical or different.

By the abovementioned heteroaryl groups are meant 6-membered heteroaryl groups containing one, two or three nitrogen atoms, or 5-membered heteroaryl groups which may contain one to four heteroatoms such as, for example, nitrogen, oxygen and sulphur, while hydrogen atoms bound to nitrogen may optionally be replaced by C_{1-3}-alkyl groups.

Preferred compounds of the above general formula I are those wherein

n denotes the number 3, 4 or 5,

m denotes the number 2 or 3,

X denotes a carbon-carbon bond, an oxygen atom, a methylene, ethylene, imino or N-(C_{1-3}-alkyl)-imino group,

R_a denotes a phenyl group or heteroaryl group substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a hydroxy group, a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly

or partly replaced by fluorine atoms, a phenoxy, heteroaryloxy, phenyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkyl-amino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group, while the abovementioned phenyl or heteroaryl moieties of the group R_1 may be substituted by one to five fluorine, chlorine or bromine atoms, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a hydroxy group, or a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, and

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or

R_1 and R_2 together represent a methylenedioxy group,

or R_a denotes a monocyclic heteroaryl or phenyl group which is substituted in each case by a phenyl or monocyclic heteroaryl group, while the abovementioned phenyl groups and heteroaryl groups may in each case be substituted by a fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, by a hydroxy, or C_{1-3}-alkoxy group,

R_b and R_c independently of one another denote a hydrogen atom or a C_{1-3}-alkyl group and

R_f and R_g, which may be identical or different, denote hydrogen atoms, C_{1-6}-alkyl groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, C_{3-7}-cycloalkyl groups, phenyl, heteroaryl, phenyl-C_{1-3}-alkyl or heteroaryl-C_{1-3}-alkyl groups, while the abovementioned phenyl groups and heteroaryl groups may in each case be substituted by one to three fluorine, chlorine or bromine atoms, by one to three C_{1-3}-alkyl groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, by one to three hydroxy groups, one to three C_{1-3}-alkoxy groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, N,N-di-(C_{1-3}-alkyl)-amino, nitro or amino group, or

R_f and R_g together with the nitrogen atom between them denote a 3- to 7-membered cycloalkyleneimino group, while the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may additionally be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group,

the isomers and the salts thereof.

Particularly preferred compounds of the above general formula I are those wherein

n denotes the number 3, 4 or 5,

m denotes the number 2 or 3,

X denotes a carbon-carbon bond or an oxygen atom,

R_a is as hereinbefore defined, and

R_b and R_c independently of one another denote a hydrogen atom or a methyl group and

R_f denotes a hydrogen atom, a C_{1-6}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a C_{3-7}-cycloalkyl group, phenyl, heteroaryl, phenyl-C_{1-3}-alkyl or heteroaryl-C_{1-3}-alkyl group, while the abovementioned phenyl groups and heteroaryl groups may in each case be substituted by one to three fluorine, chlorine or bromine atoms, by one to three C_{1-3}-alkyl groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, by one to three hydroxy groups, one to three C_{1-3}-alkoxy groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or by a nitro or amino group, and

R_g denotes a hydrogen atom,

the isomers and the salts thereof.

The following are mentioned as examples of particularly valuable compounds:

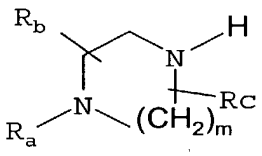
(a) 9-[4-(4-biphenyl-3-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide and

(b) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide,

the isomers and the salts thereof.

According to the invention, the new compounds are obtained by methods known from the literature, for example by the following methods:

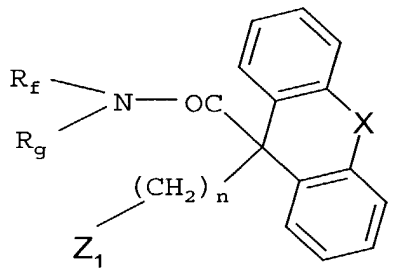
a. reacting a compound of general formula



, (II)

wherein

R_a , R_b and R_c are as hereinbefore defined, with a compound of general formula



, (III)

wherein

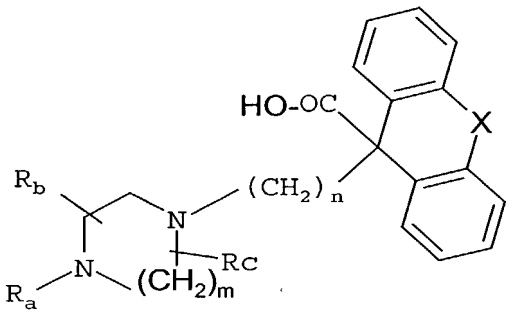
n, R_f, R_g and the tricyclic system are as hereinbefore defined and

Z_1 denotes a nucleofugic leaving group such as a halogen atom, e.g. a chlorine, bromine or iodine atom.

The reaction is preferably carried out in a solvent such as methylene chloride, acetonitrile, tetrahydrofuran, toluene, acetone/water, dimethylformamide or dimethylsulphoxide, optionally in the presence of a base such as sodium hydride,

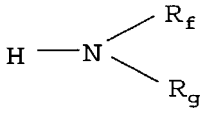
potassium carbonate, potassium tert-butoxide or N-ethyl-diisopropylamine at temperatures between 0 and 100°C, preferably at temperatures between 10 and 60°C.

b. reacting a compound of general formula



, (IV)

wherein
the tricyclic system is as hereinbefore defined, with an amine of general formula



, (V)

wherein
R_f and R_g are as hereinbefore defined, or with the reactive derivatives thereof.

The reaction is expediently carried out with a corresponding halide or anhydride of general formula IV in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxane, benzene, toluene, acetonitrile or sulfolane, optionally in the presence of an inorganic or organic base at temperatures between -20 and 200°C, but preferably at temperatures between -10 and 160°C. It may also,

however, be carried out with the free acid, optionally in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, hydrogen chloride, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexyl carbodiimide/N-hydroxysuccinimide or 1-hydroxybenzotriazole, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, at temperatures between -20 and 200°C, but preferably at temperatures between -10 and 160°C.

If according to the invention a compound of general formula I is obtained which contains a nitro group, it may be converted by reduction into a corresponding amino compound or

if a compound of general formula I is obtained wherein R_f denotes a hydrogen atom, it may be converted by alkylation into a corresponding compound wherein R_f denotes a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group.

The subsequent reduction of a nitro group is expediently carried out hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as platinum, palladium/charcoal or Raney nickel in a suitable solvent such as methanol, ethanol, ethyl acetate, tetrahydrofuran, dioxane, dimethylformamide or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid and at a hydrogen pressure of 1 to 7 bar, but preferably 1 to 5 bar, with metals such as iron, tin or zinc in the presence of an acid such as acetic acid or hydrochloric acid, with salts such as iron(II)sulphate, tin (II) chloride, sodium sulphide, sodium hydrogen sulphite or

sodium dithionite, or with hydrazine in the presence of Raney nickel at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 60°C.

The subsequent alkylation is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran, dioxane, dimethylsulphoxide or sulfolane with an alkylating agent such as a corresponding halide or sulphonic acid ester, e.g. with methyl iodide, ethyl bromide, dimethylsulphate or benzyl chloride, optionally in the presence of a tertiary organic base or in the presence of an inorganic base, expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

In the reactions described hereinbefore, any reactive groups present such as hydroxy, carboxy, amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for a hydroxy group may be a trimethylsilyl, tert.butyl-dimethylsilyl, acetyl, benzoyl, methyl, ethyl, tert.butyl, trityl, benzyl or tetrahydropyranyl group,

a protecting group for a carboxyl group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group and

protecting groups for an amino, alkylamino or imino group may be a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl

or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide or aprotically, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C. However, a silyl group may also be cleaved using tetrabutylammonium fluoride as described hereinbefore.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved for example hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 60°C, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar. A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with iodotrimethylsilane, optionally using a solvent such as methylene chloride, dioxane, methanol or diethyl ether.

A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid at temperatures between 50 and 120°C or by treating with sodium hydroxide solution, optionally in the presence of a solvent such as tetrahydrofuran at temperatures between 0 and 50°C.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20 and 50°C.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the cis/trans mixtures may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as racemates may be separated by methods known per se (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known per se, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be, for example, (+) or (-)-menthol and an optically active acyl group in amides may be, for example, a (+)-or (-)-menthyloxycarbonyl.

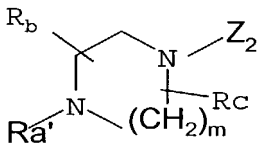
Furthermore, the compounds of formula I obtained may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, if the new compounds of formula I thus obtained contain an acidic group such as a carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts

thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds of general formulae II to VI used as starting materials are known from the literature in some cases or may be obtained by methods known from the literature or are described in the Examples.

The compounds of general formula II are obtained, for example, by reacting a compound of general formula



, (VI)

wherein R_b and R_c are as hereinbefore defined, Z_2 denotes a protecting group for an amino group, e.g. the tert.butoxycarbonyl or benzyloxycarbonyl group, and R_a' denotes, for example, a phenyl or monocyclic heteroaryl group substituted by a bromine or iodine atom, with a, for example, trifluoromethyl-substituted monocyclic aryl or heteroaryl group which is additionally substituted by a boric acid group, in the presence of a catalyst such as palladium acetate, a base such as potassium tert.butoxide and a phase transfer catalyst such as tetrabutylammonium iodide in a solvent such as water, DMF, toluene or mixtures thereof at temperatures of between 20 and 130°C. The protecting group is cleaved by methods known from the literature and leads to a compound of general formula II.

A compound of general formula III is obtained, for example, by reacting a corresponding disubstituted carboxylic acid with an α,ω-dihaloalkane in the presence of a strong base such as lithium diisopropylamide, sodium amide or sodium hydride and subsequently reacting the carboxylic acid with a corresponding amine.

As already mentioned hereinbefore, the compounds of general formula I and the physiologically acceptable salts thereof have valuable pharmacological properties. In particular, they are valuable inhibitors of the microsomal triglyceride-transfer protein (MTP) and are therefore suitable for lowering the plasma levels of the atherogenic lipoproteins.

For example, the compounds according to the invention were investigated for their biological effects as follows:

Inhibitors of MTP were identified by a cell-free MTP activity kit. Solubilised liver microsomes from various species (e.g. rat, pig) could be used as the MTP source. To prepare donor and acceptor vesicles, lipids dissolved in organic solvents were mixed in suitable proportions and applied in a thin layer to the wall of a glass container by blowing the solvent in a nitrogen current. The solution used to prepare donor vesicles contained 400 µM phosphatidylcholine, 75 µM cardiolipin and 10 µM [^{14}C]-triolein (68.8 µCi/mg). To prepare acceptor vesicles, a solution of 1.2 mM phosphatidylcholine, 5 µM triolein and 15 µM [^{3}H]-dipalmitoylphosphatidylcholine (108 mCi/mg) was used. Vesicles are formed by wetting the dried lipids with test buffer and then subjecting to ultrasound. Vesicle populations of uniform size were obtained by gel filtration of the ultrasonicated lipids. The MTP activity test contains

donor vesicles, acceptor vesicles and the MTP source in test buffer. Substances were added from concentrated DMSO-containing stock solutions; the final concentration of DMSO in the test was 0.1%. The reaction was started by the addition of MTP. After a suitable incubation period the transfer process was stopped by the addition of 500 µl of a SOURCE 30Q anion exchanger suspension (Pharmacia Biotech). The mixture was shaken for 5 minutes and the donor vesicles bound to the anion exchanger material were separated off by centrifuging. The radioactivity of [3H] and [14C] found in the supernatant was determined by liquid scintillation measurement and from this the recovery of the acceptor vesicles and the triglyceride transfer rate were calculated.

In view of the abovementioned biological properties the compounds of general formula I and the physiologically acceptable salts thereof are particularly suitable for lowering the plasma concentration of atherogenic apolipoprotein B (apoB)-containing lipoproteins such as chylomicrons and/or very low density lipoproteins (VLDL) as well as the residues thereof such as low density lipoproteins (LDL) and/or lipoprotein(a) (Lp(a)), for treating hyperlipidaemias, for preventing and treating atherosclerosis and the clinical sequela thereof, and for preventing and treating related disorders such as diabetes mellitus, adiposity and pancreatitis, oral administration being preferred.

The daily dose needed to achieve such an effect is between 0.5 and 500 mg, expediently between 1 and 350 mg, but preferably between 5 and 200 mg, in adults.

For this purpose, the compounds of formula I prepared according to the invention, optionally combined with other active substances such as other lipid-lowering agents, for example HMG-CoA-reductase inhibitors, cholesterol biosynthesis inhibitors such as squalene synthase inhibitors and squalene cyclase inhibitors, bile acid-binding resins, fibrates, cholesterol resorption inhibitors, niacin, probucol, CETP inhibitors and ACAT inhibitors may be incorporated together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The Examples that follow are intended to illustrate the invention:

Example 1

9-[4-(4-phenyl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoro-ethyl)-amide

a. 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid

89 ml (0.11 mol) of a 1.6 M butyllithium solution in hexane are added dropwise at 0°C to a solution of 21 g (0.1 mol) of 9-fluorenecarboxylic acid in 700 ml tetrahydrofuran under nitrogen and stirred for one hour. Then, still at 0°C, 13.13 ml (0.11 mol) of dibromobutane are added and the solution is stirred for 30 hours at ambient temperature. After this time, 50 ml of water are added and the mixture is stirred for 30 minutes. The solution is evaporated down, combined with water and extracted with 250 ml of diethyl ether. The aqueous phase is acidified with 150 ml of 1N hydrochloric acid and extracted three times with 250 ml of dichloromethane. The combined organic phases are dried over sodium sulphate and the solvent is removed.

Yield: 18.5 g (53.6 % of theoretical),

Melting point: 123°C

b. 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid chloride

23 g (0.067 mol) of 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid are dissolved in 40 ml dichloromethane and combined with three drops of dimethylformamide and 6.96 ml (0.081 mol) of oxalyl chloride, dissolved in 10 ml dichloromethane, under nitrogen at 0°C. The mixture is stirred for 3 hours at ambient temperature. Then the solvent is removed and the crude product is further reacted without any more purification.

Yield: 24 g (99 % of theoretical)

c. 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

23 g (0.063 mol) of 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid chloride are added dropwise at 0°C under nitrogen to a solution of 9.35 g (0.069 mol) of 2,2,2-trifluoroethylamine-hydrochloride and 26 ml (0.188 mol) of triethylamine in 550 ml of dichloromethane and stirred for 2 hours at ambient temperature. The reaction mixture is extracted twice with water, 1N hydrochloric acid and sodium hydrogen carbonate solution. The organic phase is dried over sodium sulphate and the solvent is distilled off. Purification is by column chromatography on silica gel (eluant: cyclohexane/ethyl acetate = 8:1).
Yield: 15.8 g (58.6 % of theoretical),
Melting point: 172°C

d. 9-[4-(4-phenyl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoro-ethyl)-amide

A suspension of 0.,4 g (0.93 mmol) of 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide, 0.153 ml (1 mmol) of 1-phenylpiperazine, 0.8 g of potassium carbonate and 1 ml water in 30 ml dimethylformamide is stirred for 10 hours at 80°C. The reaction mixture is then poured onto water, extracted with ethyl acetate and the organic phase is dried over sodium sulphate. Purification is by column chromatography on silica gel (eluant: dichloromethane/methanol = 15:1).
Yield: 0.1 g (19.7 % of theoretical),
Melting point: 127-128°C

Example 2

9-[4-(4-biphenyl-3-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

a. 1-biphenyl-3-yl-piperazin-dihydrochloride

A suspension of 1 g (4.29 mmol) of 3-bromobiphenyl, 2.2 g (25.54 mmol) of piperazine and 2.499 g (26 mmol) of sodium tert.butoxide in 40 ml toluene is heated to 80 *[sic]* under nitrogen. Then 0.01 g (0.011 mmol) of tris(dibenzylidene-acetone)dipalladium(0) and 0.02 g (0.032 mmol) of BINAP are added, the mixture is heated to 86 *[sic]* for 7 hours and stirred for 14 hours at ambient temperature. Water and ethyl acetate are added in succession, the organic phase is separated off, dried over sodium sulphate and evaporated down. The residue is combined with an ethereal hydrochloric acid solution and diisopropyl ether and the precipitate formed is filtered off.

Yield: 1.05 g (78.6 % of theoretical),

Melting point: 219-221°C

$C_{16}H_{18}N_2$ (M = 238.34)

Calc.: molpeak $(M+H)^+$: 239

Found: molpeak $(M+H)^+$: 239

b. 9-[4-(4-biphenyl-3-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

A suspension of 0.2 g (0.643 mmol) of 1-biphenyl-3-yl-piperazine-dihydrochloride, 0.256 g (0.6 mmol)of 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide and 0.1 g potassium carbonate in 20 ml of acetonitrile and 0.1 ml of water is stirred for 24 hours at 60°C. The reaction mixture is poured onto water, extracted with ethyl acetate and dried

over sodium sulphate. Purification is by column chromatography on silica gel (eluant: dichloromethane/ethanol = 30:1).
Yield: 0.2 g (53.3 % of theoretical),
$C_{36}H_{36}F_3N_3O$ (M = 583.70)
Calc.: molpeak $(M)^+$: 583
Found: molpeak $(M)^+$: 583

Example 3

9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

a. 1-Benzyl-4-biphenyl-4-yl-piperazine

1.6 ml (0.05 mol) of butyllithium solution in n-hexane is added dropwise to a solution of 8.81 g (0.05 mol) of 1-benzylpiperazine in 50 ml of anhydrous THF under argon at 0°C and stirred for one hour. Then 9.21 g (0.05 mol) of 4-methoxybiphenyl are added and the reaction mixture is refluxed for 12 hours. The solvent is then evaporated off, the residue is combined with 150 ml of 2 N hydrochloric acid followed by diethyl ether and the precipitate formed is filtered off. The precipitate is washed with diethyl ether, suspended in 20 % sodium carbonate solution and extracted several times with dichloromethane. After drying over magnesium sulphate the solvent is removed and the residue is washed with ethyl acetate and diethyl ether.
Yield: 12.5 g (85 % of theoretical)
Melting point: 146-148°C

b. 1-biphenyl-4-yl-piperazine

A suspension of 12.45 g (0.037 mol) of 1-benzyl-4-biphenyl-4-yl-piperazine and 4 g of palladium hydroxide in 360 ml of

methanol is stirred for 6 hours at ambient temperature in a Parr apparatus under a hydrogen pressure of 50 psi. The catalyst is separated off and the filtrate is evaporated down.
Yield: 8.64 g (95.6 % of theoretical),
Melting point: 134-138°C

c. 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

A solution of 0.4 g (1.678 mmol) of 1-biphenyl-4-yl-piperazine, 0.682 g (1.6 mmol) of 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide and 0.223 ml (1.6 mmol) of triethylamine in 20 ml acetonitrile is stirred for 14 hours at 60°C and then diluted with water. It is extracted with ethyl acetate and the organic phase is dried over sodium sulphate. Purification is by column chromatography on silica gel (eluant: dichloromethane/ ethanol = 40:1).
Yield: 0.29 g (29.6 % of theoretical),
Melting point: 209-211°C
$C_{36}H_{36}F_3N_3O$ (M = 583.70)
Calc.: molpeak $(M)^+$: 583
Found: molpeak $(M)^+$: 583

Example 4

9-{4-[4-(4-Chloro-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(4-chloro-phenyl)-piperazine dihydrochloride and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.
Yield: 0.2 g (54.3 % of theoretical),
Melting point: 166°C
$C_{30}H_{31}ClF_3N_3O$ (M = 542.049)

Calc.: molpeak $(M)^+$: 541/543

Found: molpeak $(M)^+$: 541/543

Example 5

9-{4-[4-(3-Chloro-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(3-chlorophenyl)-piperazine dihydrochloride and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.09 g (16.5 % of theoretical),

Melting point: 122°C

$C_{30}H_{31}ClF_3N_3O$ (M = 542.049)

Calc.: molpeak $(M+H)^+$: 542/544

Found: molpeak $(M+H)^+$: 542/544

Example 6

9-{4-[4-(4-Benzyloxy-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(4-benzyloxy-phenyl)-piperazine hydrochloride and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.21 g (48.6 % of theoretical),

Melting point: 180°C

$C_{37}H_{38}F_3N_3O_2$ (M = 613.73)

Calc.: molpeak $(M+H)^+$: 614

Found: molpeak $(M+H)^+$: 614.

Example 7

9-{4-[4-(4-Trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(4-trifluoromethyl-phenyl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.23 g (48.7 % of theoretical)

Melting point: 176°C

$C_{31}H_{31}F_6N_3O$ (M = 575.60)

Calc.: molpeak $(M+H)^+$: 576

Found: molpeak $(M+H)^+$: 576

Example 8

9-{4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(3-trifluoromethyl-phenyl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.16 g (33.9 % of theoretical)

$C_{31}H_{31}F_6N_3O$ (M = 575.60)

Calc.: molpeak $(M+H)^+$: 576

Found: molpeak $(M+H)^+$: 576

Example 9

9-{4-[4-(4-Fluorophenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(4-fluorophenyl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.1 g (23.2 % of theoretical)

Melting point: 116-117°C

$C_{30}H_{31}F_4N_3O$ (M = 525.59)

Calc.: molpeak $(M+H)^+$: 526

Found: molpeak $(M+H)^+$: 526

Example 10

9-{4-[4-(4-Chloro-3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(4-chloro-3-trifluoromethyl-phenyl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.13 g (26 % of theoretical)

Melting point: 96°C

$C_{31}H_{30}ClF_6N_3O$ (M = 610.04)

Calc.: molpeak $(M+H)^+$: 608/610

Found: molpeak $(M+H)^+$: 608/610

Example 11

9-{4-[4-(4-methyl-phenyl)-3-methyl-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(4-methyl-phenyl)-3-methyl-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.17 g (38.7 % of theoretical)

$C_{32}H_{36}F_3N_3O$ (M = 535.65)

Calc.: molpeak $(M)^+$: 535

Found: molpeak $(M)^+$: 535

Example 12

9-{4-[4-(3,4-dichlorophenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(3,4-dichlorophenyl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.15 g (31.7 % of theoretical)

Melting point: 122°C

$C_{30}H_{30}Cl_2F_3N_3O$ (M = 576.49)

Calc.: molpeak $(M)^+$: 575/577/579

Found: molpeak $(M)^+$: 575/577/579

Example 13

9-{4-[4-(4-methoxy-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(4-methoxy-phenyl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.2 g (52.8 % of theoretical)

Melting point: 120°C

$C_{31}H_{34}F_3N_3O_2$ (M = 537.63)

Calc.: molpeak $(M+H)^+$: 538

Found: molpeak $(M+H)^+$: 538

Example 14

9-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(2-methoxy-phenyl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.1 g (18.6 % of theoretical)

$C_{31}H_{34}F_3N_3O_2$ (M = 537.63)

Calc.: molpeak $(M+H)^+$: 538

Found: molpeak $(M+H)^+$: 538

Example 15

9-{4-[4-(2,4-Dimethoxy-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(2,4-dimethoxy-phenyl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.15 g (37.5 % of theoretical)

$C_{32}H_{36}F_3N_3O_3$ (M = 567.65)

Calc.: molpeak $(M+H)^+$: 568

Found: molpeak $(M+H)^+$: 568

Example 16

9-{4-[4-(5-Chloro-2-methoxy-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(5-chloro-2-methoxy-phenyl)-piperazine hydrochloride and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.11 g (27.3 % of theoretical)

$C_{31}H_{33}ClF_3N_3O_2$ (M = 572.07)

Calc.: molpeak $(M+H)^+$: 572/574

Found: molpeak $(M+H)^+$: 572/574

Example 17

9-{4-[4-(4-nitro-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(4-nitro-phenyl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.35 g (38.6 % of theoretical)

Melting point: 146°C

$C_{30}H_{31}F_3N_4O_3$ (M = 552.60)

Calc.: molpeak $(M)^+$: 552

Found: molpeak $(M)^+$: 552

Example 18

9-{4-[4-(4-amino-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide hydrochloride

A solution of 0.25 g (0.45 mmol) of 9-{4-[4-(4-nitro-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide in a mixture of 20 ml of ethyl acetate and 10 ml of methanol is hydrogenated in the presence of 0.1 g of palladium on charcoal. Then the catalyst is filtered off, the solvent is distilled off and the residue is dissolved in ethanol. After the addition of ethanolic hydrochloric acid solution the solvent is distilled off.

Yield: 0.15 g (59.4 % of theoretical)

Melting point: >270°C

$C_{30}H_{33}F_3N_4O$ X HCl (M = 559.08)

Calc.: molpeak $(M+H)^+$: 523

Found: molpeak $(M+H)^+$: 523

Example 19

9-{4-[4-(2-methyl-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(2-methyl-phenyl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.21 g (57.2 % of theoretical)

$C_{31}H_{34}F_3N_3O$ (M = 521.63)

Calc.: molpeak $(M+H)^+$: 522

Found: molpeak $(M+H)^+$: 522

Example 20

9-{4-[4-Pyridin-2-yl-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-pyridin-2-yl-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.15 g (35.9 % of theoretical)

Melting point: 123°C

$C_{29}H_{31}F_3N_4O$ (M = 508.59)

Calc.: molpeak $(M+H)^+$: 509

Found: molpeak $(M+H)^+$: 509

Example 21

9-{4-[4-(6-methoxy-pyridin-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(6-methoxy-pyridin-2-yl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.38 g (60.1 % of theoretical)

Melting point: 131°C

$C_{30}H_{33}F_3N_4O_2$ (M = 538.61)

Calc.: molpeak (M-H): 537

Found: molpeak (M-H): 537

Example 22

9-{4-[4-(6-methoxy-pyridin-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-4-fluorobenzyl-amide

Prepared analogously to Example 2 b from 1-(6-methoxy-pyridin-2-yl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-4-fluorobenzyl-amide.

Yield: 0.05 g (10 % of theoretical)

$C_{35}H_{37}FN_4O_2$ (M = 564.70)

Calc.: molpeak (M-H): 563

Found: molpeak (M-H): 563

Example 23

9-{4-[4-(6-methoxy-pyridin-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-4-methoxybenzyl-amide

Prepared analogously to Example 2 b from 1-(6-methoxy-pyridin-2-yl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-4-methoxybenzyl-amide.

Yield: 0.02 g (8 % of theoretical)

$C_{36}H_{40}N_4O_3$ (M = 576.74)

Calc.: molpeak $(M+H)^+$: 577

Found: molpeak $(M+H)^+$: 577

Example 24

9-{4-[4-(6-ethoxy-pyridin-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(6-ethoxy-pyridin-2-yl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.03 g (8.5 % of theoretical)

$C_{31}H_{35}F_3N_4O_2$ (M = 552.64)

Calc.: molpeak $(M+H)^+$: 553

Found: molpeak $(M+H)^+$: 553

Example 25

9-{4-[4-(6-methyl-pyridin-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(6-methyl-pyridin-2-yl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.04 g (7.7 % of theoretical)

Melting point: 85-87°C

$C_{30}H_{33}F_3N_4O$ (M = 522.61)

Calc.: molpeak $(M+H)^+$: 523

Found: molpeak $(M+H)^+$: 523

Example 26

9-{4-[4-(6-methyl-pyridin-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-4-fluorobenzyl-amide

Prepared analogously to Example 2 b from 1-(6-methyl-pyridin-2-yl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-4-fluorobenzyl-amide.

Yield: 0.16 g (44 % of theoretical)

Melting point: 96-97°C

$C_{35}H_{37}FN_4O$ (M = 548.71)

Calc.: molpeak $(M+H)^+$: 549

Found: molpeak $(M+H)^+$: 549

Example 27

9-{4-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.19 g (33 % of theoretical)

Melting point: 147-149°C

$C_{30}H_{30}F_6N_4O$ (M = 576.59)

Calc.: molpeak $(M+H)^+$: 577

Found: molpeak $(M+H)^+$: 577

Example 28

9-{4-[4-(6-phenyl-pyridin-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

a. tert.butyl 4-(6-bromo-pyridin-2-yl)-piperazine-1-carboxylate

A solution of 4 g (16.88 mmol) of 2,6-dibromopyridine, 3.14 g (16.88 mmol) of tert.butyl piperazine-1-carboxylate and 5.89 ml (33.77 mmol) of N,N-diisopropylethylamine in 30 ml of n-butanol is refluxed for eight hours. The solvent is then distilled off. Purification is by column chromatography on silica gel (eluant: cyclohexane/ethyl acetate = 2:1).
Yield: 2.2 g (38.1 % of theoretical)
Melting point: 95°C
$C_{30}H_{30}F_6N_4O$ (M = 576.59)
Calc.: molpeak $(M+H)^+$: 577
Found: molpeak $(M+H)^+$: 577

b. tert.butyl 4-(6-phenyl-pyridin-2-yl)-piperazine-1-carboxylate

A mixture of 2 g (5.84 mmol) of tert.butyl 4-(6-bromo-pyridin-2-yl)-piperazine-1-carboxylate, 0.75 g (6.15 mmol) of phenylboric acid, 2.66 g (17.52 mmol) of caesium fluoride, 0.045 g (0.15 mmol) of 2-(di-t-butylphosphino)-biphenyl and 0.013 g (0.06 mmol) of palladium acetate in 20 ml of dioxane is stirred for six hours at 50°C under nitrogen. Then it is diluted with water and the reaction mixture is extracted with ethyl acetate. The organic phase is separated off and dried over sodium sulphate. Purification is by column chromatography on silica gel (eluant: cyclohexane/ethyl acetate = 4:1).
Yield: 0.7 g (35.3 % of theoretical)

$C_{20}H_{25}N_3O_2$ (M = 339.44)

Calc.: molpeak $(M+Na)^+$: 362

Found: molpeak $(M+Na)^+$: 362

b. *[sic]* 1-(6-phenyl-pyridin-2-yl)-piperazine

A solution of 0.7 g (2.06 mmol) of tert.butyl 4-(6-phenyl-pyridin-2-yl)-piperazine-1-carboxylate and 3 ml of trifluoroacetic acid in 30 ml of dichloromethane is stirred for three hours at ambient temperature. The solvent is then distilled off, the residue is combined with water and made basic with sodium hydroxide solution. It is then extracted with dichloromethane and the organic phase is separated off and dried over sodium sulphate.

Yield: 0.4 g (81.1 % of theoretical)

$C_{15}H_{17}N_3$ (M = 239.32)

Calc.: molpeak $(M+H)^+$: 240

Found: molpeak $(M+H)^+$: 240

d. 9-{4-[4-(6-phenyl-pyridin-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(6-phenyl-pyridin-2-yl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.05 g (17.1 % of theoretical)

Melting point: 63°C

$C_{35}H_{35}F_3N_4O$ (M = 584.69)

Calc.: molpeak $(M+H)^+$: 585

Found: molpeak $(M+H)^+$: 585

Example 29

9-{4-[4-(4-phenyl-pyridin-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(4-phenyl-pyridin-2-yl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.11 g (26.7 % of theoretical)

Melting point: 59°C

$C_{35}H_{35}F_3N_4O$ (M = 584.69)

Calc.: molpeak $(M+H)^+$: 585

Found: molpeak $(M+H)^+$: 585

Example 30

9-{4-[4-(6-phenoxy-pyridin-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

a. 2-Chloro-6-phenoxy-pyridine

A reaction mixture consisting of 1.48 g (10 mmol) of 2,6-dichloropyridine, 6 g (63.75 mmol) of phenol and 2.4 g (60 mmol) of sodium hydroxide in 10 ml of water is heated to 140°C for 24 hours in a bomb. After cooling the reaction mixture is made strongly alkaline with sodium hydroxide solution and extracted with dichloromethane. The organic phase is separated off and dried over sodium sulphate. Purification is by column chromatography on silica gel (eluant: cyclohexane/ethyl acetate = 3:1).

Yield: 0.3 g (14.6 % of theoretical)

$C_{11}H_8ClNO$ (M = 205.64)

Calc.: molpeak $(M+H)^+$: 205/207

Found: molpeak $(M+H)^+$: 205/207

b. 9-{4-[4-(6-phenoxy-pyridin-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 2-chloro-6-phenoxy-pyridine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.045 g (15.4 % of theoretical)

$C_{35}H_{35}F_3N_4O_2$ (M = 600.69)

Calc.: molpeak $(M+H)^+$: 601

Found: molpeak $(M+H)^+$: 601

Example 31

9-(4-{4-[6-(4-Chloro-phenoxy)-pyridin-2-yl]-piperazin-1-yl}-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-[6-(4-chloro-phenoxy)-pyridin-2-yl]-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.04 g (15.1 % of theoretical)

$C_{35}H_{34}ClF_3N_4O_2$ (M = 635.13)

Calc.: molpeak $(M+H)^+$: 635/637

Found: molpeak $(M+H)^+$: 635/637

Example 32

9-(4-{4-[6-(3-Chloro-phenoxy)-pyridin-2-yl]-piperazin-1-yl}-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-[6-(3-chloro-phenoxy)-pyridin-2-yl]-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.04 g (15.1 % of theoretical)

$C_{35}H_{34}ClF_3N_4O_2$ (M = 635.13)

Calc.: molpeak $(M+H)^+$: 635/637

Found: molpeak $(M+H)^+$: 635/637

Example 33

9-(4-{4-[6-(2-Chloro-phenoxy)-pyridin-2-yl]-piperazin-1-yl}-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-[6-(2-chloro-phenoxy)-pyridin-2-yl]-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.06 g (22.7 % of theoretical)

$C_{35}H_{34}ClF_3N_4O_2$ (M = 635.13)

Calc.: molpeak $(M)^+$: 634/636

Found: molpeak $(M)^+$: 634/636

Example 34

9-(4-{4-[6-(4-methoxy-phenoxy)-pyridin-2-yl]-piperazin-1-yl}-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-[6-(4-methoxy-phenoxy)-pyridin-2-yl]-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.03 g (11.2 % of theoretical)

$C_{36}H_{37}F_3N_4O_3$ (M = 630.71)

Calc.: molpeak $(M+H)^+$: 631

Found: molpeak $(M+H)^+$: 631

Example 35

9-{4-[4-(6-methoxy-pyridin-2-yl)-piperazin-1-yl]-butyl}-9H-xanthene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(6-methoxy-pyridin-2-yl)-piperazine and 9-(4-bromo-butyl)-9H-xanthene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.17 g (45.2 % of theoretical)

Melting point: 122°C

$C_{30}H_{33}F_3N_4O_3$ (M = 554.61)

Calc.: molpeak $(M+H)^+$: 555

Found: molpeak $(M+H)^+$: 555

Example 36

9-{4-[4-(6-methoxy-pyridin-2-yl)-2,6-dimethyl-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(6-methoxy-pyridin-2-yl)-3,5-dimethyl-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.07 g (13.2 % of theoretical)

Melting point: 122°C

$C_{32}H_{37}F_3N_4O_2$ (M = 566.67)

Calc.: molpeak $(M+H)^+$: 567

Found: molpeak $(M+H)^+$: 567

Example 37

9-{4-[4-(6-methoxy-pyridin-2-yl)-2,6-dimethyl-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-4-fluorobenzyl-amide

Prepared analogously to Example 2 b from 1-(6-methoxy-pyridin-2-yl)-3,5-dimethyl-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-4-fluorobenzyl-amide.

Yield: 0.16 g (40.7 % of theoretical)

Melting point: 78-79°C

$C_{37}H_{41}FN_4O_2$ (M = 592.76)

Calc.: molpeak (M-H): 591

Found: molpeak (M-H): 591

Example 38

9-{4-[4-(3-phenyl-[1,2,4]thiadiazol-5-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Prepared analogously to Example 2 b from 1-(3-phenyl-[1,2,4]thiadiazol-5-yl)-piperazine and 9-(4-bromo-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide.

Yield: 0.05 g (23.4 % of theoretical)

Melting point: 115°C

$C_{32}H_{32}F_3N_5OS$ (M = 591.70)

Calc:	C: 64.95	H: 5.46	N: 11.84	S: 5.42	F: 9.63
Found:	C: 64,92	H: 5.73	N: 11.50	S: 5.70	F: 9.28

The following compounds may be prepared analogously to Examples 1 to 38:

(1) 9-{4-[4-(4'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(2) 9-{4-[4-(3'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(3) 9-{4-[4-(2'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(4) 9-{4-[4-(4'-chlorobiphenyl-4-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(5) 9-{4-[4-(3'-chlorobiphenyl-4-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(6) 9-{4-[4-(2'-chlorobiphenyl-4-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(7) 9-{4-[4-(4'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(8) 9-{4-[4-(3'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(9)9-{4-[4-(2'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(10) 9-{4-[4-(4'-methyl-biphenyl-4-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(11) 9-{4-[4-(3'-methyl-biphenyl-4-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(12) 9-{4-[4-(2'-methyl-biphenyl-4-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(13) 9-{4-[4-(4'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(14) 9-{4-[4-(3'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(15) 9-{4-[4-(2'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(16) 9-{4-[4-(4'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(17) 9-{4-[4-(3'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(18) 9-{4-[4-(2'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(19) 9-{4-[4-(4'-chlorobiphenyl-3-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(20) 9-{4-[4-(3'-chlorobiphenyl-3-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(21) 9-{4-[4-(2'-chlorobiphenyl-3-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(22) 9-{4-[4-(4'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(23) 9-{4-[4-(3'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(24) 9-{4-[4-(2'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(25) 9-{4-[4-(4'-methyl-biphenyl-3-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(26) 9-{4-[4-(3'-methyl-biphenyl-3-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(27) 9-{4-[4-(2'-methyl-biphenyl-3-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(28) 9-{4-[4-(4'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(29) 9-{4-[4-(3'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(30) 9-{4-[4-(2'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(31) 9-{4-[4-(3-Thiazol-2-yl-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(32) 9-{4-[4-(3-Thiophen-3-yl-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(33) 9-(4-{4-[3-(1H-imidazol-4-yl)-phenyl]-piperazin-1-yl}-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(34) 9-(4-{4-[3-(1H-Pyrrol-2-yl)-phenyl]-piperazin-1-yl}-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(35) 9-{4-[4-(4-Thiazol-2-yl-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(36) 9-{4-[4-(4-Thiophen-3-yl-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(37) 9-(4-{4-[4-(1H-imidazol-4-yl)-phenyl]-piperazin-1-yl}-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(38) 9-(4-{4-[4-(1H-Pyrrol-2-yl)-phenyl]-piperazin-1-yl}-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(39) 9-{4-[4-(4-Pyridin-2-yl-phenyl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(40) 9-{4-[4-(6-phenyl-pyridin-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(41) 9-{4-[4-(4-phenyl-pyrimidin-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(42) 9-{4-[4-(2-phenyl-pyrimidin-5-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(43) 9-{4-[4-(5-phenyl-pyridin-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(44) 9-{4-[4-(5-phenyl-thiophen-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(45) 9-{4-[4-(5-phenyl-oxazol-2-yl)-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(46) 9-[4-(4-[2,2']Bipyridinyl-6-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(47) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-methylamide

(48) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-ethylamide

(49) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-propylamide

(50) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-isopropylamide

(51) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-benzylamide

(52) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-phenylamide

(53) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(pyridin-2-yl)-amide

(54) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(4-fluorophenyl)-amide

(55) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(3-chlorophenyl)-amide

(56) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-dimethylamide

(57) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-diethylamide

(58) {9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-yl}-aziridin-1-yl-methanone

(59) {9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-yl}-azetidin-1-yl-methanone

(60) {9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-yl}-pyrrolidin-1-yl-methanone

(61) {9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-yl}-piperidin-1-yl-methanone

(62) {9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-yl}-morpholin-1-yl-methanone

(63) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-2-fluoro-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(64) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-2-methyl-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(65) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-2-chloro-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(66) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-3-methoxy-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(67) 9-[4-(4-biphenyl-3-yl-piperazin-1-yl)-butyl]-2-fluoro-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(68) 9-[4-(4-biphenyl-3-yl-piperazin-1-yl)-butyl]-2-methyl-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(69) 9-[4-(4-biphenyl-3-yl-piperazin-1-yl)-butyl]-2-chloro-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(70) 9-[4-(4-biphenyl-3-yl-piperazin-1-yl)-butyl]-3-methoxy-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(71) 9-[3-(4-biphenyl-4-yl-piperazin-1-yl)-propyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(72) 9-[3-(4-biphenyl-3-yl-piperazin-1-yl)-propyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(73) 9-{4-[4-(6-methoxy-pyridin-2-yl)-2-(R,S)-methyl-piperazin-1-yl]-butyl}-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(74) 9-{4-[4-(5-trifluoromethyl-pyridin-2-yl)-[1,4]diazepan-1-yl]-butyl}-9-H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

(75) 9-(5-{4-[6-(pyridin-3-yloxy)-pyridin-2-yl]-piperazin-1-yl}-pentyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide

Example 40

Tablets containing 5 mg of active substance per tablet

Composition:

active substance	5.0 mg
lactose monohydrate	70.8 mg
microcrystalline cellulose	40.0 mg
sodium carboxymethylcellulose, insolubly crosslinked	3.0 mg
magnesium stearate	1.2 mg

Preparation:

The active substance is mixed for 15 minutes with lactose monohydrate, microcrystalline cellulose and sodium carboxymethylcellulose in a suitable diffusion mixer. Magnesium stearate is added and mixed with the other substances for another 3 minutes.

The finished mixture is compressed in a tablet press to form facetted flat round tablets.

Diameter of the tablet: 7 mm
Weight of a tablet: 120 mg

Example 41

Capsules containing 50 mg of active substance per capsule

Composition:

active substance	50.0 mg
lactose monohydrate	130.0 mg
corn starch	65.0 mg
highly dispersed silicon dioxide	2.5 mg
magnesium stearate	2.5 mg

Preparation:

A starch paste is prepared by swelling some of the corn starch in a suitable amount of hot water. The paste is then left to cool to room temperature.

The active substance is premixed for 15 minutes in a suitable mixer with lactose monohydrate and corn starch. The starch paste is added and the mixture is mixed with sufficient water to produce a moist homogeneous mass. The moist mass is passed through a screen with a mesh size of 1.6 mm. The screened granules are dried on racks at about 55°C for 12 hours.

The dried granules are then passed through screens with mesh sizes of 1.2 and 0.8 mm. Highly dispersed silica is mixed with the granules in a suitable mixer for 3 minutes. Then magnesium

stearate is added and mixing is continued for another 3 minutes.

The finished mixture is packed into empty size 1 hard gelatine capsule shells using a capsule filling machine.

Example 42

Tablets containing 200 mg of active substance per tablet

Composition:

active substance	200.0 mg
lactose-monohydrate	167.0 mg
microcrystalline cellulose	80.0 mg
hydroxypropyl-methylcellulose, type 2910	10.0 mg
poly-1-vinyl-2-pyrrolidone, insolubly crosslinked	20.0 mg
magnesium stearate	3.0 mg

Preparation:

HPMC is dispersed in hot water. After cooling, the mixture yields a clear solution.

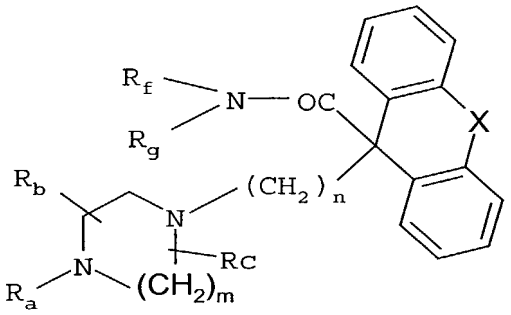
The active substance is premixed in a suitable mixer for 5 minutes with lactose monohydrate and microcrystalline cellulose. The HPMC solution is added and the mixing is continued until a homogeneous moist composition is obtained. The moist composition is passed through a screen with a mesh size of 1.6 mm. The screened granules are dried on racks at about 55°C for 12 hours.

The dried granules are then passed through screens with mesh sizes of 1.2 and 0.8 mm. Poly-1-vinyl-2-pyrrolidone is mixed with the granules in a suitable mixer for 3 minutes. Then magnesium stearate is added and mixing is continued for another 3 minutes.

The finished mixture is compressed in a tablet press to form oblong tablets (16.2 x 7.9 mm).
Weight of a tablet: 480 mg

Patent Claims

1. Substituted piperazine derivatives of general formula



, (I)

wherein

n denotes the number 1, 2, 3, 4 or 5,

m denotes the number 2 or 3,

X denotes a carbon-carbon bond, an oxygen atom, a methylene, ethylene, imino or N-(C_{1-3}-alkyl)-imino group,

R_a denotes a phenyl group or heteroaryl group substituted by the groups R_1 and R_2, wherein

> R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a hydroxy group, a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a phenoxy, heteroaryloxy, phenyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, nitro, amino,

C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkyl-amino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonyl-amino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group, while the abovementioned phenyl or heteroaryl moieties of the group R_1 may be substituted by one to five fluorine, chlorine or bromine atoms, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a hydroxy group, or a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, and

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or

R_1 and R_2 together represent a methylenedioxy group,

or R_a denotes a monocyclic heteroaryl or phenyl group which is substituted in each case by a phenyl or monocyclic heteroaryl group, while the abovementioned phenyl groups and heteroaryl groups may in each case be substituted by a fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, amino-carbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group,

R_b and R_c independently of one another denote a hydrogen atom or a C_{1-3}-alkyl group and

R_f and R_g, which may be identical or different, denote hydrogen atoms, C_{1-6}-alkyl groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, C_{3-7}-cycloalkyl groups, phenyl, heteroaryl, phenyl-C_{1-3}-alkyl or heteroaryl-C_{1-3}-alkyl groups, while the abovementioned phenyl groups and heteroaryl groups may in each case be substituted by one to three fluorine, chlorine or bromine atoms, by one to three C_{1-3}-alkyl groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, by one to three hydroxy groups, one to three C_{1-3}-alkoxy groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, N,N-di-(C_{1-3}-alkyl)-amino, nitro or amino group, or

R_f and R_g together with the nitrogen atom between them denote a 3- to 7-membered cycloalkyleneimino group, while the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may additionally be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group,

while the tricyclic group in the abovementioned general formula I may be mono- or disubstituted by fluorine or chlorine atoms, by methyl or methoxy groups and the substituents may be identical or different,

and by the abovementioned heteroaryl groups are meant 6-membered heteroaryl groups containing one, two or three nitrogen atoms, or 5-membered heteroaryl groups which may contain one to four heteroatoms such as, for example, nitrogen, oxygen and sulphur, while hydrogen atoms bound to nitrogen may optionally be replaced by C_{1-3}-alkyl groups,

the isomers and the salts thereof.

2. Substituted piperazine derivatives of general formula I according to claim 1, wherein

n denotes the number 3, 4 or 5,

m denotes the number 2 or 3,

X denotes a carbon-carbon bond, an oxygen atom, a methylene, ethylene, imino or N-(C_{1-3}-alkyl)-imino group,

R_a denotes a phenyl group or heteroaryl group substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a hydroxy group, a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a phenoxy, heteroaryloxy, phenyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkyl-amino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group, while the abovementioned phenyl or heteroaryl moieties of the group R_1 may be substituted by one to five fluorine, chlorine or bromine atoms, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a hydroxy

group, or a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, and

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or

R_1 and R_2 together represent a methylenedioxy group,

or R_a denotes a monocyclic heteroaryl or phenyl group which is substituted in each case by a phenyl or monocyclic heteroaryl group, while the abovementioned phenyl groups and heteroaryl groups may in each case be substituted by a fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, by a hydroxy, or C_{1-3}-alkoxy group,

R_b and R_c independently of one another denote a hydrogen atom or a C_{1-3}-alkyl group and

R_f and R_g, which may be identical or different, denote hydrogen atoms, C_{1-6}-alkyl groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, C_{3-7}-cycloalkyl groups, phenyl, heteroaryl, phenyl-C_{1-3}-alkyl or heteroaryl-C_{1-3}-alkyl groups, while the abovementioned phenyl groups and heteroaryl groups may in each case be substituted by one to three fluorine, chlorine or bromine atoms, by one to three C_{1-3}-alkyl groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, by one to three hydroxy groups, one to three C_{1-3}-alkoxy groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or

by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, N,N-di-(C_{1-3}-alkyl)-amino, nitro or amino group, or

R_f and R_g together with the nitrogen atom between them denote a 3- to 7-membered cycloalkyleneimino group, while the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may additionally be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group,

the isomers and the salts thereof.

3. Substituted piperazine derivatives of general formula I according to claim 1, wherein

n denotes the number 3, 4 or 5,

m denotes the number 2 or 3,

X denotes a carbon-carbon bond or an oxygen atom,

R_a is defined as in claim 2, and

R_b and R_c independently of one another denote a hydrogen atom or a methyl group and

R_f denotes a hydrogen atom, a C_{1-6}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a C_{3-7}-cycloalkyl group, phenyl, heteroaryl, phenyl-C_{1-3}-alkyl or heteroaryl-C_{1-3}-alkyl group, while the abovementioned phenyl groups and heteroaryl groups may in each case be substituted by one to three fluorine, chlorine or

bromine atoms, by one to three C_{1-3}-alkyl groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, by one to three hydroxy groups, one to three C_{1-3}-alkoxy groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or by a nitro or amino group, and

R_g denotes a hydrogen atom,

the isomers and the salts thereof.

4. Substituted piperazine derivatives of general formula I according to claim 1, wherein

n denotes the number 4,
m denotes the number 2,

X denotes a carbon-carbon bond or an oxygen atom,

R_a denotes a phenyl group or heteroaryl group substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, fluorine or chlorine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a C_{1-4}-alkoxy group, a phenoxy group, a phenyl-C_{1-3}-alkoxy or a nitro or amino group,

wherein the abovementioned phenyl moiety of the phenoxy group may be substituted by a chlorine atom or by a methoxy group,

R_2 denotes a hydrogen atom, a chlorine atom or a C_1-C_4-alkoxy group,

or R_a denotes a monocyclic heteroaryl or phenyl group which is substituted in each case by a phenyl group,

R_b and R_c independently of one another denote a hydrogen atom or a C_{1-3}-alkyl group and

R_f denotes a C_1-C_6-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a phenyl-C_{1-3}-alkyl group, while the abovementioned phenyl group may be substituted in each case by a fluorine atom or by a C_1-C_3-alkoxy group, and

R_g denotes a hydrogen atom,

the isomers and the salts thereof.

5. The following substituted piperazine derivatives of general formula I according to claim 1:

(a) 9-[4-(4-biphenyl-3-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide and

(b) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide,

the isomers and the salts thereof.

6. Physiologically acceptable salts of the compounds according to claims 1 to 5.

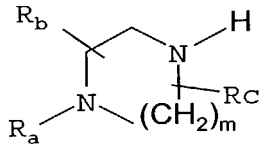
7. Medicaments, containing a compound according to at least one of claims 1 to 5 or a salt according to claim 6 optionally together with one or more inert carriers and/or diluents.

8. Use of a compound according to at least one of claims 1 to 5 or a salt according to claim 6 for the preparation of a medicament having a lowering effect on the plasma levels of atherogenic lipoproteins.

9. Process for preparing a medicament according to claim 6, characterised in that a compound according to at least one of claims 1 to 4 or a salt according to claim 5 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

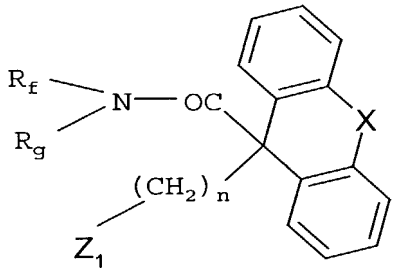
10. Process for preparing the compounds according to claims 1 to 6, characterised in that

a. a compound of general formula



, (II)

wherein
R_a, R_b and R_c are defined as in claims 1 to 4, is reacted with a compound of general formula



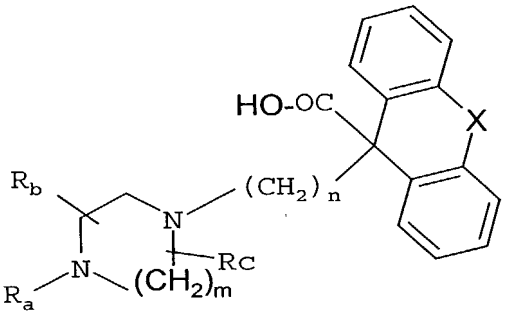
, (III)

wherein

n, R_f, R_g and the tricyclic system are defined as in claims 1 to 4 and

Z_1 denotes a nucleofugic leaving group, or

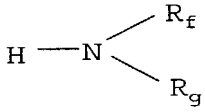
b. a compound of general formula



, (IV)

wherein

the tricyclic system is defined as in claims 1 to 4, is reacted with an amine of general formula



, (V)

wherein
R_f and R_g are defined as in claims 1 to 4, or with the reactive derivatives thereof and

if desired a compound of general formula I thus obtained which contains a nitro group is converted by reduction into a corresponding amino compound and/or

a compound of general formula I thus obtained wherein R_f denotes a hydrogen atom is converted by alkylation into a corresponding compound wherein R_f denotes a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group, and/or

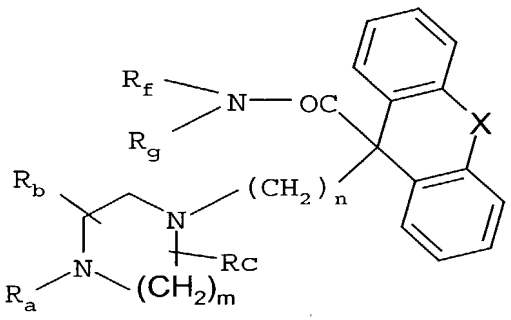
any protecting group using to protect reactive groups during the reactions is cleaved and/or

a compound of general formula I thus obtained is resolved into its stereoisomers and/or

a compound of general formula I thus obtained is converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts thereof with an inorganic or organic acid or base.

Abstract

The present invention relates to substituted piperazine derivatives of general formula



, (I)

wherein

R_a, R_b, R_c R_f, R_g and m, n and X are defined as in claim 1, the isomers and salts thereof, particularly the physiologically acceptable salts thereof, which are valuable inhibitors of the microsomal triglyceride-transfer protein (MTP), medicaments containing these compounds and their use, as well as the preparation thereof.

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing **OR** ☑ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	5/1272PCT
First Named Inventor	Thorsten LEHMANN-LINTZ
COMPLETE IF KNOWN	
Application Number	10 / 089,024
Filing Date	To Be Assigned
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

SUBSTITUTED PIPERAZINE DERIVATIVES, THE PREPARATION THEREOF AND THEIR USE AS MEDICAMENTS

(Title of the Invention)

the specification of which
☐ is attached hereto
OR
☑ was filed on (MM/DD/YYYY) 09/19/2000 as United States Application Number or PCT International Application Number PCT/EP00/09146 and was amended on (MM/DD/YYYY) _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1 56

I hereby claim foreign priority benefits under 35 U S C 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	Certified Copy Attached? NO
DE 199 45 594.5	Germany	09/23/1999	☐	☐	☑
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto

I hereby claim the benefit under 35 U.S.C 119(e) of any United States provisional application(s) listed below

Application Number(s)	Filing Date (MM/DD/YYYY)

☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U S C 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1 56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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OR

☑ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number
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Alan R. Stempel	28,991	Philip I. Datlow	41,482
Mary-Ellen M. Devlin	27,928	Timothy X. Witkowski	40,232
Anthony P. Bottino	41,629	David A. Dow	46,124

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto

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Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
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Inventor's Signature						Date	06/03/2001
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Post Office Address	Ameisenberg 1						
Post Office Address							
City	Ochsenhausen	State		ZIP	D-88416	Country	Germany

☑ Additional inventors are being named on the 1 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 1 of 1

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Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

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Mailing Address _____

City Biberach State _____ ZIP D-88400 Country Germany

Case No. 5/1272PCT

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DECLARATION — Supplemental Priority Data Sheet

Additional foreign applications:

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
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